Pharmacologic Treatment of Tension-type Headache,Cluster Headache, and TACs

Thomas N. Ward MD
Professor of Medicine (Neurology)
Dartmouth Medical School
June 2008

Advice

- Be sure of the diagnosis before selecting treatment
- Do not mistake a treatment response for a diagnosis
- Know the ICHD-II
- Suggested texts: The Headaches (3rd ed.), Comprehensive Review of Headache Medicine (written for the Headache Boards), Headache in Clinical Practice (2nd ed.)

Tension-Type Headache (TTH)

- Remember TTH in migraineurs is different than TTH in non-migraineurs (Spectrum study/Cady).
- Not particularly well-studied.
- Not often seen in clinic (episodic form).
- Some chronic TTH is truly refractory (could this be NDPH admixed with CTTH?).

® American Headache Society

Episodic TTH (ETTH).

- Patients usually self-medicate. Patients come to clinic if symptoms are unresponsive to OTCs or worsen.
- Association with stress, anxiety.
- NSAIDs are the drugs of first choice.
- The following have good evidence of efficacy: acetaminophen 1000 mg, aspirin 650 mg (dose-response shows 1000 mg better), ibuprofen especially 800 mg, ketoprofen, naproxen and naproxen sodium, diclofenac potassium, im ketorolac

ETTH treatment

- 50 mg ketoprofen > 200 mg ibuprofen=1000mg acetaminophen
- Low 2 hour pain-free rates (<35%)
- Among NSAIDs ibuprofen may have the lowest rate of GI bleeding.
- Adding caffeine (e.g. 130-200 mg) clearly effective
- Some old evidence for adding meprobamate (metabolite of carisoprodol)
- Peripheral muscle relaxants are ineffective (no evidence and risk of habituation).

Factoids

- Problems with combination analgesics: medication overuse headache, headache chronification, medication dependency. Use with caution/set limits.
- Triptans in TTH: work if the patient is a migraineur. Sumatriptan sc has a small effect in TTH (non-migraineurs) but oral form does not

® American Headache Society

Chronic Tension-type Headache (CTTH)

- Those who come to clinic may be difficult too treat.
- ? NDPH mixed in (review this in ICHD-II)
- Address medication-overuse if present
- Look for co-morbidities (psychiatric, physical)
- Remember to utilize behavioral modalities.
- Amitriptyline is the only proven pharmacologic therapy!!!!!!!
- NSAIDs are unproven in CTTH and carry significant risks.

Amitriptyline

- Mechanisms: inhibits presynaptic reuptake of serotonin and NE, blocks muscarinic cholinergic receptors, blocks H_1 receptors, α_1-adrenergic receptors, 5-HT_2 receptors. Potentiates endogenous opioids. Possible NMDA receptor antagonist.
- T ½ 13-36 hours. Metabolism slower in the elderly.
- No relationship between plasma concentration and analgesic effect.
- Benefit often independent of antidepressant effect.

Other Therapies for CTTH

- Lower-grade evidence for maprotiline 75mg per day, and for mirtazepine.
- Botulinum toxin has no evidence (and actually good evidence that it is ineffective for CTTH (Silberstein)).
- Tizanidine: centrally-acting muscle relaxant (α_2-adrenergic agonist). Some evidence that it is effective in CTTH in women (2-6 mg tid).

  Lowers plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) which is elevated in CTTH

® American Headache Society

Cluster Headache

- Acute and chronic forms
- As headache pain is maximal at onset, need rapidly-acting treatments
- Oral narcotics are not appropriate

Treatment: Cluster HA

- Acute: sc sumatriptan 4 or 6 mg (4 mg is tid)
- Oxygen properly given: 100% FIO2 at 7 or more liters/minute by mask
- Others: intranasal lidocaine, intranasal zolmitriptan
- Dihydroergotamine iv, other ergots
- Watch out for narcotics: transnasal butorphanol

Prevention: Cluster

- Methysergide 2mg tid or more (methylergonovine is metabolite of methysergide 0.2mg tid or more)
- Verapamil: the best; may need to go to 480 mg per day or more. EKGs
- Occipital nerve block
- Steroids
- Lithium (sometimes added to verapamil) 300mg/day or more
- Valproate, topiramate, others
- ? melatonin

® American Headache Society

? Hormones

- Stillman: testosterone replacement for low/borderline low levels
- Rozen: clomiphene (one case cluster, one case SUNCT)

Desperate patients

- Admit: repetitive iv dihydroergotamine (Raskin protocol)

Cluster Headache DDx

- 4.5 Hypnic Headache (not a TAC)
- "alarm clock headache": attacks of dull HA that always awaken the patient from sleep. Occur >15 times/month, last at least 15 minutes, usually occur in those >50yo
- No autonomic features!!!!!!!
- Tx: lithium, caffeine, flunarizine, indomethacin, verapamil, methysergide

® American Headache Society

Paroxysmal Hemicrania (PH)

- Indomethacin is the treatment of choice
- May have to push the dose to 225 mg/day
- Some reports of indomethacin-unresponsive PH
- Beware PH that becomes bilateral, or unresponsive to indomethacin (or requires escalating doses)-consider secondary problems including tumor, increased intracranial pressure, medication-overuse
- Indomethacin is often poorly tolerated (use lowest effective dose, protect GI tract) (in non-headache prone patients it frequently causes headache!!).

Paroxysmal hemicrania

- Occipital nerve blocks don't work.
- On fMRI: contralateral posterior hypothalamus (?) and contralateral ventrolateral midbrain
- "Indo test"
- Other treatments: other NSAIDs, verapamil, acetazolamide
- Sumatriptan not reliably effective

SUNCT

- May have only conjunctival injection or tearing or other cranial autonomic symptoms (SUNA)
- Secondary forms due to lesions in the posterior fossa or in/near the pituitary.
- Treatment: tough. Lamotrigine, topiramate, gabapentin, iv lidocaine.

® American Headache Society

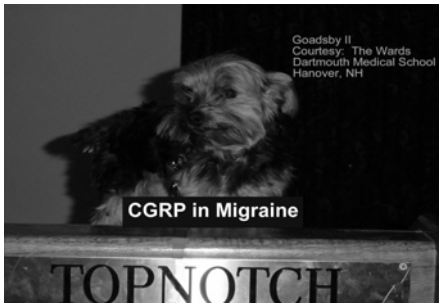
4.7 Hemicrania Continua

- Not a TAC
- Primary and secondary forms
- On fMRI contralateral posterior hypothalamus and ipsilateral ventrolateral midbrain active
- ? Episodic form
- Foreign body sensation in the eye
- "Persistent HA strictly responsive to indomethacin"

HC

- Indomethacin first choice
- Other treatments: other NSAIDs, verapamil, topiramate, melatonin, occipital nerve stimulation

Thank you very much



® American Headache Society

Pharmacologic Headache Therapy for Tension-type Headache, Cluster Headache and (other) Trigeminal Autonomic Cephalgias (TACs)

Thomas N. Ward MD
Professor of Medicine (Neurology)
Dartmouth Medical School
AHS June 2008

In this lecture I shall review pharmacologic headache therapy for cluster headache, other trigeminal autonomic cephalgias (TACs) (including hemicrania continua which is not currently classifed as a TAC) and tension-type headache. Other lectures will cover non-pharmacologic/behavioral measures and procedures. Though intentionally redundant, I have included clinical features in this handout which I will not cover during the lecture to provide context for treatment selection. I have emphasized the preventative treatment options for cluster headache particularly. I will provide several references at the end of this handout to guide your further reading.

Evidence-based guidelines from the US Headache Consortium covering data through 1997 are available at www.aan.com. There is little evidence for treating special populations (children, the elderly, and pregnancy/lactation). Also, much of the literature on treating cluster and tension-type headaches is of limited quality.

The mechanism(s) of action for preventative drugs in headache is unknown. Currently inhibition of cortical spreading depression is favored for most if not all agents used in migraine. Drugs may also enhance antinociception, block neurogenic inflammation and inhibit peripheral and/or central sensitization. There may be effects on the biologic clock in the hypothalamus.

In cluster headache it is very important not to miss this diagnosis as the pain of cluster headache is said to be the most severe of any condition. It is an opportunity to alleviate terrible suffering. It is said there is a real risk of suicide ("suicide headache") as some patients live in fear of each attack. Cluster headache is one of the conditions now termed "trigeminal autonomic cephalgias" in the International Headache Society's revised Classification of Headache Disorders (ICHD- II). This category is noted for pain in the distribution of the trigeminal nerve with associated autonomic features. Pain is typically maximal in and around the eye, although it may occur elsewhere in the head and neck, even shoulder, as well.

Cluster headache attacks usually last 15-180 minutes (typically about 45 minutes) and occur from once every other day to 8 times per day (most patients have 1-3 attacks per day). These attacks are maximal in severity at or within 15 minutes of onset. It is common for some of the attacks to awaken the patient from sleep. Therefore acute therapies must be rapid in onset of efficacy. In the more common episodic form, there are bouts of attacks lasting weeks to a few months, separated by remissions lasting several months or longer. The chronic form is characterized by a lack of remissions. While it may occur at any age and in both genders, middle-aged males are most often afflicted.

During bouts, the pain remains lateralized to one side and is usually maximal at or near the eye. Associated autonomic symptoms include ipsilateral partial Horner's

® American Headache Society

syndrome, conjunctival injection, lacrimation, nasal stuffiness, and rhinorrhea. The attacks are usually briefer than migraines, and nausea and vomiting are uncommon. Auras have been reported but are not typical (aura is not unique to migraine). The behavior of the patients during an attack is often markedly different than migraineurs. Cluster sufferers may be agitated and may pace about. Another feature of cluster headaches is their periodicity, suggesting dysfunction of the biologic clock in the hypothalamus. For a particular sufferer the attacks tend to occur at the same time of day, and bouts may recur at certain times of the year. During bouts, cluster attacks may be set off by nitroglycerin, histamine or alcohol.

It should be made clear that migraine and cluster are two separate conditions although some patients have had both types of headache (just not simultaneously). Overlapping features may cause diagnostic confusion. An entity called "cyclic migraine" which is migraine with periodic occurrence has been described (and lithium has been advocated as treatment), and occasionally aura in cluster patients has been noted. Cluster patients may have nausea and vomiting, but these symptoms are not crucial to the diagnosis. Similarly, while some migraine patients manifest autonomic phenomenon due to activation of a brainstem reflex involving the superior salivatory nucleus ("sinus headache"), other features of their attacks clearly differentiate them from cluster.

Cluster headache may coexist with trigeminal neuralgia ("cluster-tic"). Features of both entities are present, such as trigger points about the face for the neuralgic component. Recognition of this situation enables correct therapy which includes measures directed against both conditions.

In cluster patients between attacks the neurologic examination is normal save for the occasional residual partial Horner's (ptosis and miosis) or tender carotid artery. Secondary causes (such as pituitary adenoma, meningioma, arteriovenous malformations) are rare but should be searched for if there are abnormalities on examination, lack of periodicity, changing pattern, persisting headache, and refractoriness to therapy (see Table 1). Imaging such as brain MRI is therefore usually unrevealing but often necessary to reassure the patient (and the clinician!) that there is no ominous intracranial process. It is my policy to always perform an MRI on all my cluster patients when first evaluated to rule out secondary cluster.

For treatment of acute attacks there are a number of choices. If there is no contraindication such as coronary artery disease, sumatriptan s.c. is almost always dramatically effective, and often even more so than for migraine (may work in less than 5-10 minutes). Subcutaneous sumatriptan has an FDA label for use in acute attacks of cluster headache. The 4mg sc dose allows for three administrations per day (as oppsed to two for the 6 mg size). Inhaled oxygen at 100% by mask at $\geq$ 7 liters per minute is also often very useful. Sometimes higher flow rates are necessary. Intranasal lidocaine at 4% has been used as it may work rapidly as has transnasal butorphanol under careful supervision. I now avoid prescribing narcotics for cluster as much as possible. Overuse and misuse are real risks. Zolmitriptan nasal spray has been used with some efficacy as has oral zolmitriptan but neither is as rapid as sumatriptan subcutaneously. Oral medications simply do not provide pain relief quickly enough.

In episodic cluster, employing prophylactic measures at the start of a bout may terminate the bout, or shorten it. A "burst" of oral steroids may be tried for 1-2 weeks, or an ipsilateral occipital nerve block may be effective. Preventative agents otherwise

® American Headache Society

employed include methysergide (not available in the US although its metabolite methylergonovine is), verapamil, and lithium. Verapamil is the agent of choice, sometimes cautiously even at doses greater than 480mg/day following EKGs. Occasionally other agents may have benefit such as valproate and topiramate. Refractory cases may respond to repetitive intravenous dihydroergotamine. Rarely, for chronic cluster patients surgery is required. Most typically, these are procedures directed against the trigeminal nerve. Deep brain stimulation (usually targeting the hypothalamus) has been used experimentally in some truly intractable cases with good results.

One reason why patients do not get better is incorrect diagnosis leading to improper treatment. Some headaches do fit cluster headache by IHS criteria but also fit those of chronic paroxysmal hemicrania (CPH). The headaches of CPH are similar to cluster attacks, except they tend to be briefer (2-30 minutes). There is overlap in the criteria and a headache of 15 to 30 minutes could therefore in some cases could be either cluster or paroxysmal hemicrania (PH) based on duration alone. Here the response to therapy made the diagnosis Like cluster headache, paroxysmal hemicrania is now divided into chronic and episodic forms depending on whether there is a remission from the daily bouts or not. It has been termed an "indomethacin-responsive syndrome" although occasionally there may be a partial response to other remedies such as aspirin, naproxen sodium or other NSAIDs. The response to indomethacin is typically rapid and dramatic. A 2 day trial at 150mg/day is usually sufficient and if no response is seen, the diagnosis is unlikely. A significant partial response warrants an increase in the dose to occasionally as much as 225 mg per day. Many patients have difficulty tolerating indomethacin. GI protective measures are warranted, as is monitoring for GI bleeding. After the headaches are controlled the dose should be tapered to the minimally effective/tolerated dose.

An uncommon, even briefer but more difficult to treat headache condition is SUNCT (Short-lasting Unilateral Neuralgiform headaches with Conjunctival injection and Tearing) and the related proposed diagnosis of SUNA (Short-lasting Unilateral Neuralgiform headaches with cranial Autonomic symptoms) found in the Appendix of the ICHD-II. Here the attacks are very frequent (up to 300 per day) and yet very brief (5-240 seconds). Diagnostic confusion with trigeminal neuralgia may occur (again the importance of accurate diagnosis!). Of course, there may also be secondary/symptomatic forms. This type of headache is said to be very difficult to control. Lamotrigine, intravenous lidocaine, topiramate, gabapentin and other drugs have been reported to have some success, and surgery has also been described. Statistically, intravenous lidocaine and lamotrigine may be the most effective.

Another condition, more loosely related to TACs, is hemicrania continua, which is defined as "Persistent strictly unilateral headache responsive to indomethacin". I include it because of the presence of autonomic features but it is not currently categorized as a TAC in the ICHD-II. Pain is daily and continuous and generally of moderate intensity (although severe exacerbations may occur). Like paroxysmal hemicrania there are often autonomic manifestations such as: 1) conjunctival injection and/or lacrimation, 2) nasal congestion and/or rhinorrhea, and 3) ptosis and/or miosis. Some patients report a foreign body sensation in the eye. Also like PH, response to indomethacin is diagnostic. Secondary causes of this headache type have also been reported. Some cases have reponded to verapamil or topiramate. Melatonin has been tried due to its structural

® American Headache Society

similarity to indomethacin (Rozen). Hemicrania continua may become bilateral in the setting of increased intracranial pressure or medication overuse.

Botulinum toxin as a headache preventative agent for any type of headache is controversial. The studies are of variable quality. There is no FDA label. There is good evidence that it does not work in tension-type headache. The PREEMPT studies are ongoing as this is written to investigate for efficacy in chronic migraine in patients not on other preventative agents. It has been used in many other headache types including cluster headache, numular headache and trigeminal neuralgia. Burstein has written on the characteristics of patients who respond to this treatment.

To repeat, there are no drugs which have an FDA label for prevention of cluster headache. Treatments are usually offered to patients with prolonged bouts in episodic cluster and for chronic cluster. Verapamil is said to be the agent of choice. Dosed higher than 480 mg/day are sometimes necessary. Lithium, valproic acid or topiramate are sometimes added to verapamil. There are some reports of response to administration of testosterone, clomiphene or melatonin. Methysergide (doses of 1-12 mg/day, occasionally higher) is sometimes used. Side effects include nausea/vomiting, muscle cramps, abdominal pain, peripheral edema. It is a vasoconstrictor and must be avoided in peripheral vascular disease and coronary artery disease. Intranasal civamide (an isomer of capsaicin) has been tested for cluster headache but the results were unimpressive.

The acute treatment of episodic tension-type headache generally offers little problem. Most patients self-treat and use over-the-counter remedies. Those who do not respond to such agents may occasionally come to the clinic. Remember that what looks like tension-type headache in migraineurs may be different (e.g. triptan-responsive) than tension-type headache in non-migraineurs. NSAIDs are the drugs of first choice. Acetaminophen is also an option. There is good evidence for this agent, ibuprofen, naproxen, ketoprofen, diclofenac, and injectable ketorolac. 2 hour pain-free rates are not impressive, however (< 35% typically). Adding caffeine clearly enhances short-term efficacy. Potential problems with combination analgesics to keep in mind include medication-overuse headache, medication dependency and chronification of headache. Peripheral muscle relaxants lack evidence of efficacy and carry a risk of habituation. Subcutaneous sumatriptan has a modest effect in tension-type headache attacks while the oral form is ineffective (unless the patient happens to be a migraineur).

Lastly, for chronic tension-type headache (CTTH) there is little evidence for any agent save for amitriptyline which has good evidence. Lack of response to multiple agents makes one wonder if patients with New Daily Persistent Headache (NDPH) which has overlapping diagnostic features with tension-type headache might have been included in early studies. Besides amitriptyline there have been reports (not rising to the level of high-grade evidence) supporting mirtazepine and maprotitline. NSAIDs are unproven in CTTH and carry GI and renal risks. Tizanidine, an α-2 adrenergic agonist, at doses of 2-6 mg tid may be effective in CTTH in women. It may act by lowering elevated levels of 3-methoxy-4-hydroxyphenylglycol (MHPG). I advocate individualized therapy including non-pharmacologic measures.

® American Headache Society

Selected References

Jakubowski M, McAllister PJ, Bajwa ZH, Ward TN, Smith P, Burtsein R. Exploding vs. imploding headache in migraine prophylaxis with Botulinum Toxin A. Pain 2006; 125(3):286-295.

Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA (eds) 2006: The Headaches. 3rd Ed. Lippincott Williams & Wilkins. Philadelphia.

Ward TN. 2006. Cluster Headache and Related Headaches. In: Levin M, Ward TN (eds): Head, Neck and Facial Pain. A Case-based Handbook of Diagnosis, Management, and Prognosis. Anadem Publishing, Columbus, Ohio. Chapter 3: 19-23.

Ward TN 2006. Headache Evaluation and Treatment. In: Holmes GL, Cohen JA, Levin M (eds): Educational Review Manual in Neurology. Castle Connolly Graduate Medical Publishing, New York, New York. Chapter 26: 769-790.

McGeeney B. Topiramate in the treatment of cluster headache. Curr Pain and Headache Rep. 2003; 7(2): 135-138.

Prizshelm T, Magnoux E, Dobson CF, Hamel E, Aubão M. Melatonin as adjunctive therapy in the prophylaxis of cluster headaches: a pilot study. Headache 2002; 42(8): 787-792.

Peres MF, Rozen TD. Melatonin in the preventative treatment of chronic cluster headache. Cephalalgia 2001; 21(10): 993-995.

Silberstein SD, Göbel H, Jensen R, et al. Botulinum toxin type A in the prophylactic treatment of chronic tension-type headache: a multicentre, double-blind, randomized, placebo-controlled, parallel-group study. Cephalalgia 2006; 26(7): 790-800.

Saper JR, Klapper J, Mathew NT, et al. Intranasal Civamide for the Treatment of Episodic Cluster Headaches. Arch Neurol 2002; 59: 990-994.

Stillman MJ. Testosterone replacement therapy for treatment of refractory cluster headache. Headache 2006; 46(6): 925-933.

Lenaerts M. Phamacoprophylaxis of tension-type headache. Curr Pain and Headache Rep 2005; 9(6): 442-447.

McGeeney B. Cluster headache pharmacotherapy. Am J Ther 2005; 12(4): 351-358.

Rozen T. Clomiphene Citrate for Treatment Refractory Chronic Cluster Headache. Headache 2008; 48(2): 286-290.

Fogelholm R, Murros K. Tizanidine in chronic tension-type headache: a placebo-controlled double-blind cross-over study. Headache 1992; 32: 509-513.

® American Headache Society

Bendtsen L. Efficacy of antidepressants in headache prophylaxis. In: Olesen J, Silberstein S, Tfelt-Hansen P (Eds.). Preventative pharmacotherapy of headache disorders. 12th ed. New York. Oxford University Press 2004:103-111.

® American Headache Society